REMARKS

A. Status of the Claims

Claims 3, 5-6, 24, 26-31, 44-68, and 74 were previously canceled and claims 13, 15-17, and 32 are canceled herein. Claims 1, 14, 75 and 76 have been amended and claim 79 has been added. Support for the amended claims can be found in the specification at least at page 10, lines 1-2; page 11, lines 22-27; page 23, lines 9-11; page 31, lines 3-6; and, originally filed claims 25 and 26. Support for added claim 79 can be found in the specification at least at page 92, lines 15-20. Claims 1, 2, 4, 7-23, 25, 32-43, 69-73, and 75-79 are therefore pending.

B. Inventorship

Applicants again request the amendment to the specification. In the previous Response to the Office Action that was filed in February 2007 ("February 2007 Response"), Applicants noted complied with the steps set forth in 37 C.F.R. §1.48, which is reproduced below.

(b) *Nonprovisional application—fewer inventors due to amendment or cancellation of claims.* If the correct inventors are named in a nonprovisional application, and the prosecution of the nonprovisional application results in the amendment or cancellation of claims so that fewer than all of the currently named inventors are the actual inventors of the invention being claimed in the nonprovisional application, an amendment must be filed requesting deletion of the name or names of the person or persons who are not inventors of the invention being claimed. Amendment of the inventorship requires:

(1) A request, signed by a party set forth in §1.33(b), to correct the inventorship that identifies the named inventor or inventors being deleted and acknowledges that the inventor's invention is no longer being claimed in the nonprovisional application; and

(2) The processing fee set forth in §1.17(i).

Applicants identified Elizabeth Grimm as an inventor being deleted because the inventor's invention was no longer being claimed in the nonprovisional patent application. More precisely, Applicants' requested "that Elizabeth Grimm be deleted as an inventor pursuant to 37 C.F.R. § 1.48(b), because the cancellation of claims during the prosecution of the present application has resulted in this person's invention no longer being claimed." The fee was set forth according to §1.17(i). All of the requirements of 1.48(b) have been fulfilled; accordingly, Applicants respectfully request again that the specification be amended as set forth above.

B. The Rejections Under 35 U.S.C. § 112, First Paragraph

The Action rejects claims 1, 2, 4, 7-23, 25, 32-43, 69-73, 75-78 as lacking enablement because it contends that only intratumoral injection is enabling. More specifically, the Action asserts that one needs to address how to deliver sufficient therapeutic agent to significant target cells. The Action further argues that the claims are not enabled because the application does not provide for targeted viral vector delivery. Applicants respectfully traverse this rejection.

The claims are directed to inhibiting angiogenesis by "providing to endothelial cells in the patient by local injection an effective amount of a human melanoma differentiation antigen-7 (MDA-7) polypeptide or a nucleic acid expressing the human MDA-7 polypeptide."

The references cited in the Office Action do not provide any evidence that the presently claimed invention is not enabled. Moreover, there is no reason to challenge that locally injecting a patient so as to provide an MDA-7 polypeptide or encoding nucleic acid will not achieve the claimed invention. Applicants point out that the claimed invention is directed to inhibiting angiogenesis by providing endothelial cells with an MDA-7 polypeptide or encoding nucleic acid. Accordingly, Applicants respectfully request that this rejection be withdrawn.

C. Claims Are Definite

The Action rejects claims 75 and 76 under 35 U.S.C. §112, second paragraph, as indefinite. More specifically, it contends that there is no antecedent basis for "viral particles" in claim 8, which refers to a "viral vector." Applicants respectfully traverse this rejection.

Applicants emphasize that the Action fails to identify any evidence to support the assertion that "the concept 'viral particle' and 'viral vector' is not equivalent to the skilled artisan in biology, and from the perspective of English language." Moreover, the relevant issue for section 112, second paragraph, is "whether a person of skill in the art can determine the scope of

the invention based on the language of the claims with "a reasonable degree of certainty." MPEP 2173.02 (citing *In re Wiggins*, 488 F.2d 538, 179 U.S.P.Q. 421 (C.C.P.A. 1973)).

Applicants contend that the specification make it clear that "viral particles" refers to an amount of "viral vector" recited in claim 8. It is simply not the convention among skilled artisans to refer to amounts of a viral vector as some number of viral vectors. "In fact, both the specification and patents issued by the USPTO make it clear that the skilled artisan refers to *an amount* of a viral vector in terms of either "plaque forming units (PFUs)" or "viral particles."

On page 9 of the specification, it states, "In certain embodiments, the nucleic acid is a viral vector, wherein the viral vector dose is or is at least 10^3, 10^4, 10^5, 10^6, 10^7, 10^8, 10^9, 10^{10}, 10^{11}, 10^{12}, 10^{13} or higher pfu or viral particles." Lines 18-20. Thus, it is clear that viral particles refers to an amount of viral vector.

Moreover, U.S. Patent No. 7,238,346 contains an issued claim that recites, "A method to obtain therapeutic levels of Factor VIII in a mammal comprising: administering less than 10^{10} infectious units of a recombinant high capacity adenoviral vector per kg of body weight or less than 10^{12} ***viral particles*** of the recombinant high capacity ***adenoviral vector*** per kg of body weight intravenously to the mammal's liver...." The usage of these terms is similar to claims 75 and 76, which demonstrates that there is a reasonable expectation that the skilled artisan would have a reasonable degree of certainty in ascertaining the scope of the rejected claims.

Applicants respectfully request this rejection be withdrawn.

D. The Rejection under 35 U.S.C. § 102(e)

The Action rejects claims 1, 2, 4, 7-23, 25, 35-43, 69-73, 75-78 are provisionally rejected under 35 U.S.C. § 102(e) as being anticipated by copending Application No. 09/615,154. Because the rejection is provisional, Applicants need not address this rejection at this time.

E. Claims Are Not Properly Rejected under 35 U.S.C. § 102(f)

The Action rejects claims 1-4, 7-23, 25, 35-43, and 69-78 under 35 U.S.C. § 102(f) over copending Application No. 09/615,154. The Action argues that because the elected invention is drawn to treating an angiogenesis-related tumor in a patient, the instant claims are anticipated by the co-pending application. Applicants respectfully traverse this rejection.

Applicants previously submitted a declaration from Sunil Chada, Rajagopal Ramesh, and Abner Mhashilkar under 37 C.F.R. § 1.132, which indicated the study of angiogenesis described in Application No. 09/615,154 is a description of the Applicants' own work. The Action stated the declaration was insufficient to overcome the rejection because it did not have Elizabeth Grimm on it. This is a result of the Action failing to acknowledge the change of inventorship on the application.

However, as indicated above, Applicants followed 37 C.F.R. §1.48 and the change in inventorship and the amendment to the specification should be entered. Accordingly, the declaration of Sunil Chada, Rajagopal Ramesh, and Abner Mhashilkar overcomes the section 102(f) rejection based on Application No. 09/615,154. *See* MPEP § 2137. Applicants, therefore, respectfully request this rejection be withdrawn.

F. Claims 1-4, 7, 8, 10-15, 24, 25, 32-36, 42, 43, 68-74, and 77 Are Not Anticipated or Obvious

The Action rejects claims 1-4, 7, 8, 10-15, 25, 32-36, 42, 43, 69-74, 77, and 78 under 35 U.S.C. § 102(e) as anticipated by or in the alternative under 35 U.S.C. § 103(a) as obvious over Fisher *et al.* (U.S. Patent 6,355,622) ("Fisher"), as evidenced by Folkman *et al.*, *Nature,* 339:58-61, 1989 and *J. Biol. Chem.*, 267:10931, 1992 ("Folkman references"). Fisher is said to teach a method of inhibiting cancer in a subject comprising intratumoral administration to nude mice bearing cervical carcinoma cells replication deficient adenoviral vector encoding full-length

mda-7 protein. The Action admits that Fisher does not literally teach that a tumor is an angiogenesis-related disease. The Action argues, however, that it was well known in the art that tumors belong to the class of angiogenesis-related diseases and that angiogenesis accompanies tumor growth and metastasis as evidenced by the Folkman references. The Action concludes that Fisher meets every limitation of the elected species, and thus, anticipates the claimed invention. Applicants respectfully traverse this rejection.

The Office Action contends that it was known in the art that adenovirus expressing MDA-7 is capable of inhibiting tumor growth. However, Fisher does not teach providing MDA-7 to any **human** endothelial cells, and consequently, it does not anticipate the claimed invention. It is not legally sufficient for anticipation that Fisher might describe inhibiting cancer cell growth of an angiogenic-dependent cancer because it does not teach a recited element of the claim. Contrary to what the Action contends, this is not a situation of claiming a new benefit to an old process because the presently claimed process is different. The difference lies in *which* cells are provided with MDA-7. Again, this difference means that Fisher does not anticipate the claimed invention.

As argued in the previous response, to the extent this rejection is premised on inherent anticipation, inherent anticipation cannot be based on probabilities or possibilities. In *MEHL/Biophile Int'l Corp. v. Milgraum,* the CAFC held that a claim that included the step of aligning a laser light applicator substantially vertically over a hair follicle opening was not inherently anticipated by a manual that taught aiming the laser at skin pigmented with tattoo ink because an operator of the laser could use the laser according to the manual without necessarily aligning the laser substantially vertically over a hair follicle opening. 192 F.3d 1362, 1365 (Fed. Cir. 1999). In *Perricone v. Medicis Pharmaceutical Corp.*, the CAFC held that claims directed to

a method for treating skin sunburn by topically applying to the skin sunburn a fatty acid ester of ascorbic acid were not inherently anticipated by a reference that disclosed topically applying the same composition to skin but not to skin sunburn. 432 F.3d 1368, 1379 (Fed. Cir. 2005).

Applicants note that "[i]nherent anticipation requires that the missing descriptive material is 'necessarily present,' not merely probably or possibly present, in the prior art." *Rosco, Inc. v. Mirror Lite Co.*, 304 F.3d 1373, 1380 (Fed. Cir. 2002). Furthermore, it is the Examiner's burden to provide a rationale or evidence to show inherency. MPEP § 2112(IV). In this case, there is no evidence that Fisher necessarily provided MDA-7 or an encoding nucleic acid to human endothelial cells.

On the issue of obviousness, Fisher nor the combination of Fisher and Roth render the claimed invention obvious because they do not teach providing MDA-7 to a human endothelial cell. A proper *prima facie* case of obviousness requires that every element of the claimed invention be accounted for in the prior art. Moreover, there is nothing in the prior art that would suggest giving MDA-7 to endothelial cells because the art taught only that MDA-7 induced apoptosis in cancer cells, not that it inhibited the differentiation of endothelial cells or led to the downregulation of CD31, as is taught by the present specification (for example, on page 98, lines 1-14 and page 99, lines 10-18). The Action provides no evidence that an apoptosis inducer like MDA-7 would have this physiological effects, and therefore, the claimed invention is not obvious.

Applicants respectfully request this rejection be withdrawn.

G. Claims 1, 7-9, 16-23, 36-41, 75, and 76 Are Not Obvious

The Action rejects claims 1, 7-9, 16-23, 36-41, 76, and 76 under 35 U.S.C. §103(a) as unpatentable over Fisher, in view of Roth (U.S. Patent 6,069,134), as evidenced by Nasz *et al.*

(Acta Microbiol Immunol Hung 48:323-48 (2001)). Applicants respectfully traverse this rejection.

The invention is directed to a method of inhibiting angiogenesis involving providing MDA-7 to human endothelial cells. The cited references simply do not teach this. A proper *prima facie* case of obviousness requires that "the prior art reference (or references when combined) must teach or suggest all the claim limitations." MPEP §2142. Furthermore, obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established. *In re Rijckaert*, 9 F.2d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993). Roth, Fisher, and Nasz do not disclose a method of inhibiting angiogenesis nor elements of this method. Consequently, a proper *prima facie* case has not been made.

Furthermore, the claimed invention was not obvious in view of Fisher because the results were surprising and unexpected. Significantly, no mention is made of angiogenesis in the Fisher reference. The focus on MDA-7 as only an apoptosis inducer is in distinct contrast to the instant application, which is why it was surprising and unexpected that MDA-7 could inhibit angiogenesis. The present specification provides specific data that the process of angiogenesis is specifically inhibited. On page 92 at lines 15-20 the specification indicates that tumors treated *in vivo* with Ad-mda7 had fewer blood vessels than untreated tumors. Furthermore, on page 99, data is provided that tumors treated with Ad-mda7 had significantly lower levels of CD31 expression, which indicates fewer blood vessels. The application also showed that MDA-7 inhibited endothelial cell differentiation *in vitro* (page 98) and inhibited tube formation (page 100).

Moreover, the present rejection cites to Roth, which involves a different tumor suppressor gene. In Roth, p53 is discussed only in the context of apoptosis as well. *See e.g.,* first paragraph of Summary of Invention. Therefore, it was surprising and unexpected that MDA-7 could inhibit angiogenesis, particularly by reducing the amount of CD31 expressed—which is indicative of fewer blood vessels in tumors—and by reducing tube formation in HUVEC cells.

Therefore, the combination of prior art references does not render obvious the claimed invention. Accordingly, Applicants respectfully request this rejection be withdrawn.

H. Double Patenting Rejection Is Provisional

Claims 1-4, 7-23, 25, 32, 35-43, 69-74, 77, and 78 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 92-116, 125-154, and 159-174 of copending U.S. Patent Application 09/615,154 ('154 application). The Action also provisionally rejects claims 1-4, 7-23, 25, 32, 35-43, 69-74, 77, and 78 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 18 and 70-74 of Application No. 10/378,590, and claims 38-41 of Application No. 11/156,521. Applicants traverse these rejections.

A method of inhibiting angiogenesis is not a species of a method of treating cancer, even if the method of inhibiting angiogenesis is in a patient with an angiogenesis-related cancer because not all cancer treatments will achieve inhibition of angiogenesis and not all cancers are angiogenesis-dependent cancers. Moreover, the current claim in the '154 application recites "providing to the patient at least one other anticancer therapy." No arguments have been provided about how this claim or any of the other pending claims of the '154 application renders obvious *each* of claims of the present applications. In addition, the Action does not provide any arguments as to how any of the claims in either the '590 application or the '521 application render obvious each of the claims of the present application, particularly in light of the fact that

claims in the present application include a step of providing MDA-7 to human endothelial cells. There is, therefore, no basis for these rejections, and Applicants respectfully request that they be withdrawn.

CONCLUSION

Applicants believe that the present document is a full and complete response to the Action dated June 19, 2007. The present case is in condition for allowance, and such favorable action is respectfully requested.

The Examiner is invited to contact the undersigned Agent at (512) 536-3081 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

Gina N. Shishima
Reg. No. 45,104
Attorney for Applicants

FULBRIGHT & JAWORSKI L.L.P.
600 Congress Avenue, Suite 2400
Austin, Texas 78701
(512) 474-5201
(512) 536-4598 (facsimile)

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